EXHIBIT 8

UNITED STATES DISTRICT COURT
DISTRICT OF MINNESOTA

In re Bair Hugger Forced Air Warming Products Liability Litigation	MDL No. 15-2666 (JNE/FLN)
This Document Relates to All Actions	EXPERT REPORT OF JONATHAN M. SAMET, M.D., M.S. March 30, 2017

I. Professional Qualifications

My education and training are in medicine (internal medicine and pulmonary disease) and public health, specifically the discipline of epidemiology (see Exhibit A – curriculum vitae). I received an A.B. degree from Harvard College in Chemistry and Physics and then received my M.D. degree from the University of Rochester School of Medicine and Dentistry. My training after medical school included completion of three years of training in the specialty of Internal Medicine and a three-year fellowship at Harvard Medical School that included training in the subspecialty of Pulmonary Medicine. I am Board certified in both, although I have not engaged in the clinical practice of medicine since 1994, when I left my position at the University of New Mexico for the then Johns Hopkins School of Hygiene and Public Health (now the Johns Hopkins Bloomberg School of Public Health). During my fellowship in clinical epidemiology at the Channing Laboratory of Harvard Medical School, I also received a master's degree in epidemiology from the Harvard School of Public Health.

Of relevance to this report, I served in the US Army from 1971-1973 as a physician. This service followed my internship in Internal Medicine at the University of Kentucky (1970-1971). Based on a critical need at the time, I received on-the-job training in anesthesiology and spent the two years of my military service as an anesthesiologist at Gorgas Hospital in the then Panama Canal Zone. The Hospital was a large facility providing care primarily for military personnel and their families, and Canal Zone employees and dependents. On a day-to-day basis, anesthesia for patients in four to six operating rooms was largely administered by nurse anesthetists under the supervision of a fully trained anesthesiologist and myself. Beyond this supervisory role, I handled many cases. Consequently, I gained extensive first-hand experience with general operating room procedures, as then practiced, covering a wide range of surgical procedures including hip replacement.

Subsequent to my fellowship training at Harvard as documented on my curriculum vitae, I have had positions at three academic institutions: the University of New Mexico School of Medicine in Albuquerque, New Mexico (1978-1994); the Johns Hopkins Bloomberg School of Public Health (1994-2008); and the University of Southern California (2008-present). At each of these institutions, I have held leadership positions including Chief of the Pulmonary and Critical Care Division of the Department of Medicine at the University of New Mexico; Chair of the Department of Epidemiology, Co-Director of the Risk Sciences and Public Policy Institute (which I co-founded), and Co-Director of the Institute for Global Tobacco Control (which I founded) of the Johns Hopkins Bloomberg School of Public Health; and Chair of the Department of Preventive Medicine of the Keck School of Medicine of USC and founding Director of the Institute for Global Health of the University of Southern California. In these positions, my responsibilities have included a mix of administration, research, education and training, and clinical practice (while at the University of New Mexico).

In general, my research activities have been centered on the health consequences of inhaled agents, such as tobacco smoke, outdoor and indoor air pollution, and radon, but also extended to the causes of cancer and the determinants of outcome for those with cancer, to cardiovascular disease and sleep-disordered breathing, and to obesity. My curriculum vitae lists my specific publications, which now number over 360 peer-reviewed research papers, approximately 400 additional publications, and 28 books and monographs.

Much of my research has addressed exposure to airborne particulate matter and the health consequences of such exposures, including the particulate progeny of radon, secondhand tobacco smoke, and particles in outdoor air. In this research, I have been involved in leading teams that have measured particle concentrations in outdoor and indoor air, and collected particles for toxicological assays. I have been involved broadly in policy issues related to indoor air quality and particulate matter, including serving on Committee 62 of the American Society of Heating, Refrigerating, and Air Conditioning Engineers (ASHRAE), which addresses ventilation of indoor spaces. For the National Research Council, I chaired the Committee on Research Priorities for Airborne Particulate Matter, the Committee on Comparative Dosimetry of Radon in Homes and Mines, and the Committee to Develop a Research Strategy for Environmental, Health, and Safety Aspects of Engineered Nanomaterials—all concerned with particles. Finally, while I was at Johns Hopkins, I was Principal Investigator for an Environmental Protection Agency funded Center for research on particulate matter.

In addition, since the 1980s, I have been involved in numerous expert panels, reports, and other activities that have involved the synthesis and evaluation of evidence for causal inference and for risk assessment, a process that typically begins with an evaluation of the evidence for existence of a hazard. Most relevant, I have been involved with the US Surgeon Generals' reports on smoking and health since 1984 in capacities including

author, consulting editor, and senior scientific editor. These reports provide authoritative determinations on the causation of disease and other adverse effects of smoking using a framework for inference that originated with the landmark 1964 report. This report established a model approach for synthesizing evidence for the purpose of reaching causal conclusions related to smoking with significant policy and public health impact. Subsequent reports have had broad impact, such as the 1986 report of Surgeon General Koop on involuntary smoke, which catalyzed the movement for clean indoor air with its conclusion that involuntary smoking caused lung cancer in never smokers. I was a Consulting Scientific Editor for this report.

As Senior Scientific Editor for the 2004 report, I led the updating of this approach to evidence evaluation and the introduction of standard language to describe the strength of evidence for causation. Across multiple reports, I have participated in the evaluation of evidence for causation as author and editor, reaching new causal conclusions in several reports, including the 1986 report (e.g., involuntary smoking causes lung cancer), the 2004 report (e.g., active smoking causes cervical cancer and cataract), and the 2014 report (e.g., active smoking causes cancer of the liver and involuntary smoking causes stroke). I was Senior Scientific Editor for both the 2004 and 2014 reports.

As a member and chair of the Clean Air Scientific Advisory Committee (CASAC) of the US Environmental Protection Agency, I provided guidance on revisions to the Agency's process for evaluating evidence and inferring causation for the major "criteria" air pollutants, such as airborne particulate matter. As chair of several committees of the National Academies of Sciences, Engineering, and Medicine, I have provided guidance on revisions to the Agency's processes for chemical risk assessment in its Integrated Risk Information System (IRIS) Program. These revisions have included introduction of formal systematic review processes and uniform approaches for assessing strength of evidence.

As an internist and pulmonary physician, I provided care for numerous patients with infectious diseases, some complicating surgery. While at Johns Hopkins, the Department of Epidemiology, which I chaired, was one of the largest academic programs in infectious disease epidemiology, providing an opportunity for me to learn much about this area from my colleagues.

II. Statement of the Question

Judgments concerning causation are made for the purposes of public health protection and health promotion at the population level. Evidence related to the causation of disease (or possibly to a benefit to health) at the population level is considered and a determination made as to whether the evidence supports the inference of a causal relationship between an agent and a particular health outcome. Such general determinations support various types of interventions intended to improve the health of

populations. Examples abound—air quality regulation, tobacco control at local, state and federal levels, and regulations covering exposures in workplaces. The determination in the 1964 Report of the Advisory Committee to the Surgeon General—that smoking causes lung cancer (in men)—is a landmark example, both for the methods used to evaluate the evidence and for the impact of the conclusion.

Distinct from population or general causation, judgments as to causation of disease in specific individuals are also made for a variety of purposes. These determinations address the question as to whether one (or more) agents contributed to the causation of disease in a specific person. The judgment is typically couched in terms of a probability statement, e.g., there is a 60 percent chance that a factor caused a particular disease in a particular person or the probability might be summarized as to whether it is more likely than not that a particular agent was causal for the individual in question.

This report addresses the topic of general causation in regard to the Bair Hugger forced-air warming devices (referred to hereafter as the Bair Hugger device), considering the full range of available and relevant evidence. The question addressed is whether use of a Bair Hugger device during hip and knee joint replacement surgeries increases risk for deep joint infections. "Risk" as used here means that the probability of deep joint infection is increased compared to what that probability would have been, absent the utilization of the Bair Hugger device during hip and knee arthroplasties. In this report, I refer to this theoretical comparison scenario of no exposure to the presence of the Bair Hugger device during surgery as the *counterfactual*. I propose that the appropriate counterfactual is either no specific warming device or the use of a warming device that does not involve forced-air, the actual alternatives in practice.

Concepts of Causation

Causal Criteria or Guidelines: The present scientific and methodological approaches used for causal inference have their origins in discussions started in the 1950s as observational epidemiological evidence emerged on the causes of "chronic diseases" (primarily cancer, cardiovascular disease, and chronic respiratory disease) related to smoking and other environmental factors. Unlike infectious diseases, for which there were necessary causal agents—i.e., the particular infecting microbes—chronic disease or non-communicable diseases generally had multiple risk factors and no one cause was necessary as for infectious diseases. Criteria (the Henle-Koch postulates) for determining if an infectious agent caused a disease in humans were proposed in the later years of the 19th century as the role of infectious organisms in human disease was established.

The Henle-Koch postulates had no direct extension to non-communicable diseases. For clear ethical and practical reasons, experiments could not be carried out to prove that cigarette smoking or other agents had adverse consequences in people. Additionally, the results of the observational studies were potentially subject to bias, including

confounding (the mixture of the effect of another factor, the confounder, with the effect of the exposure of interest), selection bias (the distortion of the true association by the way that participants are selected into study populations), and information bias (errors in the information included in a study).

The approach developed for evaluation of evidence used in the 1964 Surgeon General's report (U.S. Department of Health Education and Welfare, 1964) and in many subsequent authoritative reports, including those of the Surgeon General on smoking and health (U.S. Department of Health and Human Services, 2014), was intended to give appropriate consideration to these issues in interpreting the critical public health evidence. Consequently, systems were developed for comprehensively gathering evidence from individual epidemiological studies, assessing the potential for bias in the individual studies and the collective body of literature, and synthesizing the evidence from the studies to determine if the findings, along with evidence from other types of investigation (e.g., laboratory studies), were sufficient to support a causal conclusion: i.e., that the observed association reflected a causal process and not bias or the play of chance (Glass et al., 2013).

The landmark 1964 report of the US Surgeon General on smoking and health (U.S. Department of Health Education and Welfare, 1964) is widely regarded as providing a model approach for the systematic review of evidence in order to determine if the association between an "exposure" or "risk factor" and some health outcome(s) is causal. Key features of the approach used to develop the report and conclude that smoking causes lung cancer included:

a. The evidence then available was systematically assembled and reviewed for potential methodological concerns (e.g., confounding) and the implications of such concerns for study interpretation;
b. Multiple lines of evidence were considered including the nature and components of cigarette smoke, findings of toxicological research, epidemiological research, and data showing coherence with the hypothesis that smoking causes lung cancer, such as parallel trends of smoking and lung cancer rates in the population;
c. Development of a pragmatic definition of cause and of guidelines or criteria for evaluating evidence for causation (Table 1). Similar guidelines were proposed at about the same time by Sir Austin Bradford Hill in the United Kingdom. Of these guidelines, only temporality (i.e., cause precedes effect) must be met, but the others are critical in bolstering the case for causation and are fundamental to the weight-of-evidence approach used to evaluate the totality of the evidence available. The guidelines are not used as a checklist and all need not be met to infer causality;
d. Narrative analysis of the evidence using the guidelines to demonstrate in a transparent fashion the basis for the causal determination.

Sufficient Component Cause Framework: In considering the evidence collected for this report and the nature of the injury related to the Bair Hugger device, the sufficient-component-cause model or framework is relevant and useful. The framework provides insight into how the Bair Hugger device could increase risk for infection, when by definition an infectious organism is requisite for the occurrence of a deep joint infection. This framework considers sets of actions, events, or states of nature that together lead to the outcome under consideration. The model provides a way to account for how multiple factors combine to result in disease in an individual or population. In epidemiology, the component cause model put forward by Kenneth Rothman in a 1976 publication (Rothman, 1976) has clear applicability to considering the role of the Bair Hugger device as a causal factor. This model has broad utilization, being invoked, for example, in a recent report from a committee of the National Academies of Sciences, Engineering, and Medicine that I chaired. This report from the Committee on Using 21st Century Science to Improve Risk-Related Evaluations used the sufficient component cause framework to characterize how pathways of injury by chemicals increase risk for disease (National Academies of Sciences Engineering and Medicine, 2017).

In considering causation, causal factors are classified as to whether they are necessary or sufficient. A cause that is *sufficient* can cause disease on its own but it may not be necessary. For infectious diseases, the responsible microbial organism is necessary, but not sufficient for many infectious organisms. For example, most people who are infected with *Mycobacterium tuberculosis*, the organism responsible for clinical tuberculosis, do not develop clinical disease; the immune system is able to control the infection such that disease does not occur. For lung cancer, smoking is presently the cause of most cases (about 85%) in the United States, but smoking is not sufficient (all smokers do not develop lung cancer) nor necessary (lung cancer occurs in people who have never smoked).

In the component cause model, causal complexes that are sufficient, i.e., able to cause the outcome of concern, are represented by pies (Figure 1) with each slice being a single component of the pie, i.e., an insufficient component by itself unless the pie has only one component (Rothman and Greenland, 2005). The figure depicts three causes (I-III), each having multiple components or slices. When a cause is complete (i.e., each of its components is present), then the outcome will occur. The importance of a cause in a particular population is determined by its prevalence; different populations may have different distributions of causes, e.g., younger versus older patients or a community hospital versus a referral center. The model usefully captures multicausality in the existence of several causal pies having multiple and differing components, the dependence of the strength of component causes on the prevalence of the complementary component causes, and the interaction between component causes.

For infectious diseases by definition, the infectious organism is necessary, corresponding to component A in the example of Figure 1, which is present in causes I, II, and III.

Thus, if a necessary component cause can be eliminated, any occurrence of the outcome can be avoided. If a component is present in only one cause, the removal of that component leaves the other causes as pathways to causation. With removal of cause J, for example, cause III is eliminated but causes I and II persist. This model has ready extension to considering the role of the Bair Hugger device in causing deep joint infections, as it captures the necessary presence of the infecting agent and how additional factors contribute to risk (Figure 2).

Figure 1: Hypothetical Example of Three Sufficient Causes of Disease From: Rothman KJ, Greenland S. Causation and causal inference in epidemiology. Am J Public Health. 2005; 95 Suppl 1:S144-50.

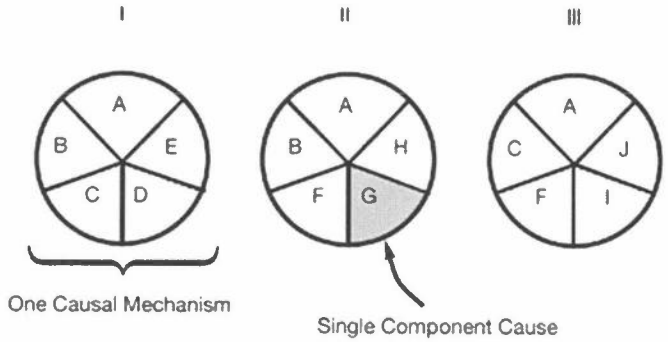


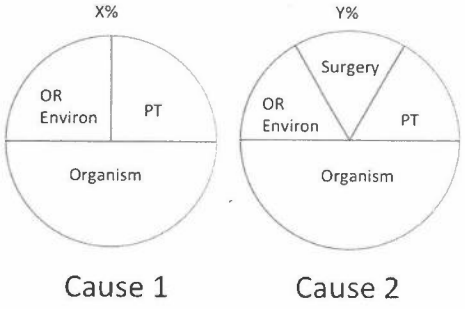
Figure 2 provides a hypothetical extension of the sufficient component cause model to deep joint infection and the role of the Bair Hugger device. It has two panels, portraying two different causal situations: the first, absent the presence of a Bair Hugger device, has two causes, each with several components; and the second, which has three causes with the addition of a cause with the Bair Hugger device as a component. Because the infecting organism is necessary, it is present in all of the causes in both panels. In the first panel (A), the first cause (Cause 1) has three general components—infecting organism, operating room environment, and patient; the second (Cause 2) has four components—infecting organism, operating room environment, patient, and surgeon. I use the terms "operating room environment," "patient," and "surgeon" in a general sense to refer to any characteristics/correlates that may influence the risk of infection. The "operating room environment" could encompass a broad range of features related to design, including air handling, operational aspects, and cleaning. Patient susceptibility factors are of evident importance and might include underlying health and immune status, smoking status, age, and relative body weight (body mass index or BMI). There are diverse pathways by which a surgeon might affect risk for infection: technique and procedure length or colonization with methicillin-resistant *Staphylococcus aureus* (MRSA).

The second panel (B) includes a third cause with four components—infecting organism, operating room environment, patient, and Bair Hugger device. The third cause includes

the Bair Hugger device, along with patient characteristics and the operating room environment. Comparison of the two panels in this hypothetical shows how the presence of the Bair Hugger device increases risk for deep joint infection, adding an additional cause to the two causes already present. The increment could be considered in absolute or relative terms: i.e., the prevalence of the additional, third cause with the Bair Hugger device or the relative increment in disease comparing the overall prevalence of the three causes in the second panel to that of the two causes in the first panel. The addition of the third circle shows how the use of the Bair Hugger device increases risk for disease; assuming the frequencies of the other two causes remain unchanged, the use of the Bair Hugger device adds an additional cause and hence more deep joint infection in comparison to the (counterfactual) scenario of only two causes. The magnitude of the increase would depend on the prevalence of the cause with the Bair Hugger device.

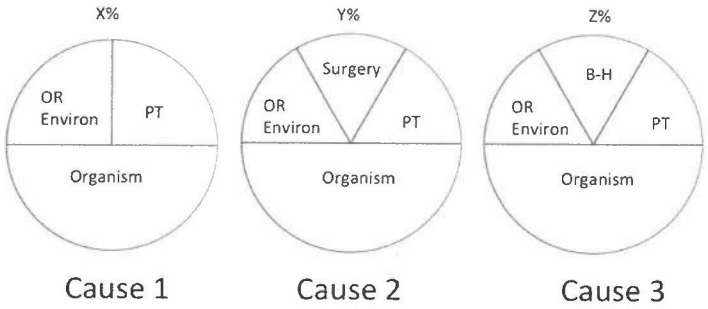
Figure 2: Adaptation of Sufficient Component Cause Model to Deep Joint Infection Risk

A: Causal Mechanisms for Deep Joint Infection without Bair-Hugger Devices



These causal pies are hypothetical and are not drawn to scale.
OR Environ = Operating Room Environment; PT = Patient;
Surgery = Surgical procedure factors

B: Causal Mechanisms for Deep Joint Infection with Bair-Hugger Devices



These causal pies are hypothetical and are not drawn to scale.
OR Environ = Operating Room Environment; PT = Patient; B-H = Bair Hugger Device
Surgery = Surgical procedure factors

With regard to the question of general causation, evidence is considered as to whether evidence supports the existence of Cause 3 in Figure 2. The model acknowledges the necessity of having an infectious organism and the contributions of patient susceptibility and other factors. It also illustrates how the existence of Cause 3 causes deep joint infections, beyond what would occur if only Causes 1 and 2 are present. Figure 2 also shows that the degree to which Cause 3 increases risk depends on the prevalence of other factors, such that the risk for deep joint infections associated with use of the Bair Hugger device could vary across institutions. Below, I review the evidence supporting the existence of a causal mechanism involving the Bair Hugger device.

III. Review of the Evidence

In writing this report, I have relied on studies from two sources: literature provided by Ciresi Conlin LLP and by literature searches conducted at USC using PubMed and the following search terms: "trends in surgical wound infections," "National AND trends AND (surgical AND would AND infection)," "Trends AND (surgical AND wound AND infection)," "Trends AND (surgical AND nosocomial AND infection)," "Trends AND (surgical AND wound AND infection) AND device," "(Patient AND warming AND device) AND (surgical AND would AND infection)," "(Patient AND warming) AND (surgical AND wound AND infection)," "(Patient AND warming AND device) AND (operating AND room)," "(Patient AND warming) AND (operating AND room)," "(Patient AND warming) AND (nosocomial AND infection)," "(Patient AND warming) AND (surgical AND site AND infection)," "microbial AND contamination AND operating AND room," "surface AND contamination AND (operating AND room)," "surface AND contamination AND (operating AND room)." The references of the main publications were also searched for additional relevant citations. I reviewed reports prepared by two of Plaintiffs' experts: Drs. William Jarvis and Said Elghobashi. Finally, I considered all the documents referenced in Exhibits B and C of this report.

Evidence Synthesis and Findings on Causation

The Range of Evidence Available: Judgments on causation of an adverse effect of an agent, whether an environmental exposure, a pharmaceutical, or a device, like the Bair Hugger device, are made on the basis of all relevant evidence, whether direct or indirect. In schemas of evidence hierarchy, randomized clinical trials are generally given the most credence, but such trials are carried out to test for efficacy of a device or therapeutic agent or the comparative efficacy or equivalence of two devices or agents. They are not generally carried out to document adverse consequences or to make a comparison of the risks of two different devices or therapeutic agents. Thus, there has not yet been a randomized clinical trial to address the potential infection risk associated with the Bair Hugger device (i.e., a trial comparing the Bair Hugger to some other warming modality). In fact, such trials would not be readily feasible in practice because of the low incidence of deep joint infections; informative sample sizes would need to be very large; and such

studies have not been reported to date. Results of a randomized controlled trial evaluating the efficacy of a device that reduces the concentration of colony-forming units (CFUs) at surgical sites were recently reported and are discussed further below (Darouiche et al., 2017).

Observational epidemiological studies have been the mainstay for investigating the causes of disease in human populations. Observational means that the study addresses the consequences of exposures as they take place in the world and that the exposures are not assigned by the researchers as in a randomized clinical trial or other type of experiment. Rather, investigators study the consequences of factors affecting health as people are exposed to those factors based on "real world" determinants. For example, observational designs were used in linking cigarette smoking to lung cancer, as some people were either current or former smokers and others had never smoked. Two basic designs were used: the case-control study comparing the smoking histories of people with lung cancer (cases) to those of similar people, but without lung cancer (controls); and the cohort study comparing the rate at which lung cancer develops in smokers over time to that in never or nonsmokers. The findings from such studies, interpreted in the context of other lines of evidence, supported the conclusion in 1964 by the Advisory Committee to the Surgeon General that smoking caused lung cancer (in men) (U.S. Department of Health Education and Welfare, 1964).

Only limited observational data are available on the potential infection risks from the Bair Hugger device, reflecting the way in which warming devices are typically purchased and used in hospitals, i.e., a hospital would generally use only a single type of warming device in its operating rooms so that comparison to another device cannot be readily made. The general research question on warming devices and infection risk has attracted limited attention to date.

On the assumption that hospitals use only a single type of warming device in operating rooms, investigation of infection risks associated with type of warming device could be carried out by classifying hospitals as to the type of warming device used and comparing deep joint infection rates for groups of hospitals classified by type of warming device used, taking other factors into account that could differ among hospitals. Such studies have not been done and would be difficult to carry out. Another approach would be to carry out a quasi-experimental study within one or more hospitals, monitoring the rate of deep joint infection over time with one device and then intentionally shifting, as abruptly as possible, to an alternative device. A change in the infection rate temporally linked to the change in device would indicate a beneficial or adverse effect of one device compared to the other. A study intentionally following this design has not been carried out, but studies have addressed changes in deep joint infection rates as changes have been made in warming equipment (discussed below).

Another line of evidence that has been evaluated is the characterization of time trends of rates of surgical site and deep joint infections. The hypothesis could be advanced that if Bair Hugger devices substantially increase deep joint infection rates, then time trends of rates of such infections should track with the timing of the introduction and utilization of the devices. This is an inherently flawed approach since it does not directly address the risks of the Bair Hugger device; the relevant data on trends are not readily available; and the consequences of other factors changing over time cannot be taken into account. The example of time trends of lung cancer in the United States illustrates the point: While incidence and mortality rates have been dropping in men for several decades because of lessening use, the risk of lung cancer in smokers has risen over this same time period (U.S. Department of Health and Human Services, 2014).

There is one directly relevant observational study in the peer-reviewed literature: the retrospective study carried out by McGovern et al. (McGovern et al., 2011). The study was based on comparing rates of deep joint infection in a hospital in the United Kingdom in two periods: one with the Bair Hugger device in use and one with conductive-fabric warming in use. Figure 7 in the publication describes the structure of the investigation: a period of exclusive use of the Bair Hugger device, a transition period, and then a period of exclusive use of conductive warming. Observation for surgical site infection, including deep joint infection, was standardized across the period of the study, but there were changes in both antibiotic prophylaxis and thromboprophylaxis. Logistic regression was used to estimate the incremental risk associated with having surgery while the Bair Hugger device was in use; the univariate estimate of the odds ratio was 3.8 and statistically significant.

This finding has been criticized as potentially reflecting confounding by the non-comparability of prophylactic antibiotic use and thromboprophylaxis in the two periods. Changes were made in both that overlapped with the different time periods described in Figure 7 of the paper. These arguments are the typical general claims made by those seeking alternative explanations for an association, and reach back to the strategies employed for decades by the tobacco industry (Proctor, 2012; Samet and Burke, 2001).

The deposition testimony of the authors of the McGovern paper addresses the issue of confounding. In an extended data set, Professor Nachtsheim compares infection rates under the two antibiotic regimes during a period when the Bair Hugger device was in use. There is no significant difference in the infection rates, indicating that one key requirement for confounding is not met: an association of the potential confounder (antibiotic use protocol) with the outcome (deep joint infection). Drs. McGovern and Reed cite additional evidence against confounding, including peer-reviewed studies indicating that different thromboprophylaxis protocols do not significantly impact deep joint infection rates (Jensen et al., 2010; Jameson et al., 2012). The authors also explain that additional data collected after publication of the McGovern study continued to

demonstrate a relative risk ratio very similar to the 3.8 odds ratio reported in the published study.

A more general argument against confounding can also be made. In setting aside whether the antibiotics and/or thromboprophylaxis were truly "confounding," the magnitude of the association (3.8 odds ratio) reported by McGovern et al. deserves consideration. For the sole explanation to lie with confounding, there would need to be sufficient positive confounding by changes in antibiotic use and/or thromboprophylaxis to explain the association fully. Such confounding is not only unlikely, but it is not supported by the evidence considered above and as reviewed by Professor Nachtsheim and Drs. McGovern and Reed. Additionally, given that the change in the warming method was temporally abrupt, confounding by other, unidentified factors seems unlikely as well. For example, the mix of patients in the time periods compared would likely be unchanged, as would factors related to the operating staff and operating rooms. The 3.8 relative risk ratio is therefore not attributable to confounding.

Other studies have been construed as "negative" and indicating safety of forced-air warming with the Bair Hugger device. In a widely used definition of safety, Lowrance (Lowrance, 1976) proposed that "A thing is safe if its risks are judged to be acceptable." This definition implies that risk can be estimated and then assessed for its acceptability. To conclude that there is no risk for deep joint infection associated with forced-air warming, an estimate of risk based on an appropriate counterfactual comparison is needed that is sufficiently precise to exclude risk levels considered unacceptable. In other words, the relative risk for deep joint infection associated with use of forced-air warming would need to be estimated along with 95% confidence intervals, as is the usual practice. The upper limit of the confidence interval would have to be below risk levels that are considered unacceptable, such as 1.5—the level at which risk is increased by 50%. To have such precision, sufficiently large studies would be needed and multiple studies would be needed to have sufficient confidence in the results. Such evidence does not exist.

Studies have been construed as indicating safety of the Bair Hugger device. However, considering the formulation of safety set out above, the studies provide findings seriously constrained by limited sample size without indicating that there is no risk with any degree of precision. Five studies are briefly described here.

1. Zink and Iaizzo (1993) assessed bacterial contamination using culture plates during simulated surgery with eight volunteers with a protocol that included two control hours and two hours with the Bair Hugger device operational. There was no significant difference in the number of bacterial colonies comparing the two periods.
2. Avidan and colleagues (1997) studied nine Bair Hugger devices and one additional device in use at their hospital. Beyond culturing the airstreams of the

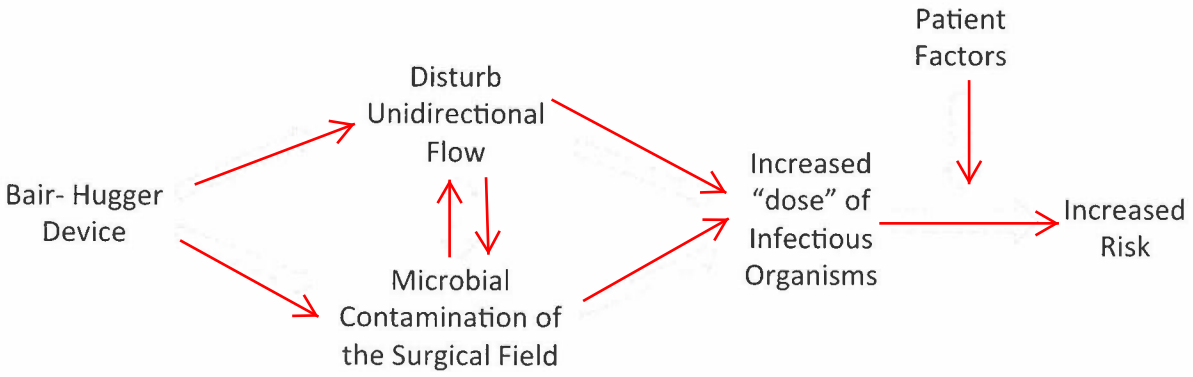
devices, several extremely limited experiments were carried out. In one experiment involving only two devices, no organisms were cultured in the exhaust air from two devices that previously tested positive for internal contamination.

3. Huang et al. (2003) measured bacteria counts at several locations and the wound site in 16 abdominal vascular procedures during which a Bair Hugger device was used. Bacterial counts dropped across the procedure.
4. Moretti et al. (2009) followed a protocol similar to that used by Huang et al. for 30 surgeries, including 20 with a Bair Hugger device. The results showed an increase in counts compared to initial at-rest conditions and a comparison is not presented of the 20 procedures with warming versus the 10 without.
5. Sessler et al. (2011) carried out a simulation study of the consequences of forced-air warming with Bair Hugger devices on tracer smoke particle counts in two operating rooms with laminar flow in place. The investigators report no significant differences in particle counts, comparing baseline and operation of the Bair Hugger devices with and without warming of the air. Data provided in Figures 2 and 3 in the published paper show increases in particle counts with the Bair Hugger device in use, particularly for the Bair Hugger model 635. The small sample size limited statistical power.

These five studies share the problem of limited sample size and statistical power. Moreover, the interpretation of the evidence by the authors is largely based on not finding statistically significant differences in small data sets. Thus, the studies do not demonstrate the safety of the Bair Hugger device. Accordingly, in terms of the larger, collective body of evidence on risk for deep joint infection, these five studies are a limited and flawed component.

The Mechanisms by which the Bair Hugger Increases Risk for Deep Joint Infection: Here, I give emphasis to the findings that address the processes by which the Bair Hugger device could increase risk for infection (Figure 3). There are two general documented mechanisms captured in Figure 3: disruption of protective unidirectional flow across the surgical field and an increased load of microorganisms in the air due to contamination of the forced-air warming device and turbulence-driven flow distributing contaminated skin flakes (squames) into the operative field. Both of these mechanisms lead to an increased number of CFUs delivered to the surgical site.

Figure 3: Mechanisms by which the Bair Hugger Device Increases Risk for Deep Joint Infection



Central to these mechanisms and risk for deep joint infection is the established relationship between the "dose" of CFUs and risk for surgical site and deep joint infection. With regard to infection risk, dose can be conceptualized as the cumulative number of CFUs that enters the surgical field, whether airborne, entering on instruments and other materials, or on the hands of surgical personnel. The dose would thus constitute the cumulative number of infectious organisms from these various routes. In Figure 3, the Bair Hugger device could increase the dose by increasing the number of airborne organisms deposited onto the surgical site or by contaminating instruments or surgical personnel as airborne CFUs settle onto these surfaces.

As reviewed by Dr. Jarvis, evidence suggests that only a small number of infectious organisms are needed to cause a deep joint infection to occur with knee and hip replacement, given the presence of a foreign material coated with a biofilm, which provides a site for growth that is not readily reached by antibiotics. Findings cited by Dr. Jarvis indicate that only a small number of organisms, possibly even a single organism, may be sufficient. A higher number of organisms reaching the implant increases the risk of infection. The randomized trial reported by Darouiche et al. (2017) further supports the concept of dose, as proposed, and the dependence of risk of deep joint infection on the number of organisms reaching the prosthesis. That study showed that reduction of CFUs reaching the surgical site with use of the Air Barrier System led to a lowering of the number of implact infections (four in the control and none in the intervention). Additionally, as noted by Dr. Jarvis, patient-associated factors are not directly causal, but can increase risk for infection as diagrammed in Figure 2.

Use of the Bair Hugger device in the operating room has two consequences that increase the dose of CFUs, and hence the risk of infection, delivered to the surgical field: disturbance of unidirectional flow across the site and an increase in microbial contamination in the operating room. A substantial literature supports both of these effects of the operation of the Bair Hugger device. With regard to disturbance of

unilateral flow, there are two lines of supporting evidence: empirical studies in operating rooms that document air flow patterns and computational fluid dynamic modeling (CFD). Plaintiffs' expert Dr. Elghobashi implemented a CFD model to describe how the operation of a forced-air warming device affects patterns of air movement within an operating room and the consequences for distribution of squames (human skin cells) during an operation—a patient undergoing knee surgery. The results of the simulation are clear, comparing the two cases—blower off and on: operation of a Bair Hugger device alters air flow and increases the numbers of squames reaching critical sites relevant to infection risk, including the surgical site and the side tables. Two studies document thermal gradients created by the Bair Hugger device that parallel the modeling of Dr. Elghobashi (Table 2).

The results of Dr. Elghobashi's modeling are paralleled by empirical studies using tracers in operating room settings (Table 3). Table 3 summarizes the results of four studies that used simulated surgical procedures to assess the impact of the operation of a Bair Hugger device versus a comparison condition on the concentration of an indicator of airborne contamination. A study by Stocks et al. (2010) supports the use of particle counts as an indicator of the potential concentration of CFUs. In this study, particle concentrations in various size bins were measured at the surgical site during 22 hip and knee procedures. The number of CFUs was also measured at the surgical site. The relationships of particle counts and several characteristics of the procedures and staff with CFUs was considered during 10-minute time blocks. Of the various particle size bins, concentration of particles 10 microns and greater was most strongly associated with CFU count, explaining 41% of the variance in CFU concentration. This finding supports the use of particle tracers and counts as a surrogate for CFUs.

A study by Legg et al. (2012) measured particle counts while the other three used tracers, including glycerol particles and detergent bubbles. All show substantial increases in concentrations/counts of the indicator, as acknowledged by 3M's 30(b)(6) witness. The report by McGovern et al. (McGovern et al., 2011) included an investigation of the effect of forced-air warming with a Bair Hugger device on disruption of unidirectional air flow using neutral-buoyancy bubbles as a marker. Two simulated procedures were included: hip replacement and a lumbar spinal procedure. The experiment provided strong evidence that use of forced-air warming, compared with conductive-fabric warming, increased bubble counts over the surgical site in both sets of simulations. The findings of Belani et al. (Belani et al., 2013) were similar.

In another simulation study, Legg et al. (2012) measured particle counts in different size ranges over the surgical site, comparing forced-air warming with conductive fabric warming and no warming. The findings showed increased particle counts in the three size bins considered versus the two comparison conditions. In a subsequent study, Legg et al. (2013) used 0.3 micron glycerol particles as the tracer and found a several thousand-fold increase in particle count associated with use of a Bair Hugger device.

The Bair Hugger device may also increase the dose of CFUs as a result of the contamination of the device by microbes and the distribution of microbes in the warmed air from the device. Evidence summarized by Dr. Jarvis supports each of these mechanisms by which the device could increase the dose of organisms delivered to the surgical site.

Findings on Causation: As noted, judgments as to causality are based on a review of the relevant lines of evidence and evaluation of the evidence within a framework for causal inference, e.g., that used in the Surgeon Generals' reports. These frameworks are not intended to be rigid and in using them, the scope and nature of the evidence available merits consideration. The relevant criteria include temporality, strength of association, consistency, and coherence. *Specificity* is not pertinent, as there are multiple factors associated with risk for deep joint infection following arthroplasty and an infectious organism is necessary. The critical and necessary requirement of *temporality* is inherently met because joint replacement and exposure to infectious organisms precede the occurrence of infection, often by months.

With regard to *strength of association*, the available observational evidence indicates a moderately strong association. The analysis reported by McGovern and colleagues documents a statistically significant association unlikely to be explained by confounding or other bias. The relative risk is estimated at 3.8. The studies summarized in Table 3 show that use of a Bair Hugger device substantially increases the concentration of various tracers over the surgical site, in fact by up to several orders of magnitude.

The guideline of *consistency* is generally applied as a consideration related to interpretation of findings of multiple observational studies and hence is not applicable to the single study by McGovern and colleagues. Here, I point to the consistency of the findings of studies addressing the effect of the Bair Hugger device on particle counts at the surgical site (see Table 3).

As discussed above, there is *coherence* across the streams of evidence supporting the model set out in Figure 3, which offers a well-supported picture of the mechanisms by which the Bair Hugger device increase risk for deep joint infection. There is a coherent body of evidence supporting both pathways. Through the pathways indicated in Figure 3, the Bair Hugger device increases the dose of microbes reaching the surgical site and an increase in this dose increases risk for deep joint infection. The study by McGovern and colleagues shows that the resulting increase in risk of deep joint infection is substantial. The evidence is thus consistent and coherent, and biological plausibility for the Bair Hugger device to increase risk for deep joint infection is well established.

In my judgment, the full body of evidence is sufficient to conclude that the Bair Hugger device causally increases risk for deep joint infection. There is sufficient consistency among the findings of the individual studies, the evidence is coherent, biological

plausibility is evident, and temporality is satisfied. As indicated in Figure 2, the Bair Hugger device is not a necessary cause, but a causal factor that increases risk of deep joint infection by adding an additional causal mechanism.

With regard to the question of how much the Bair Hugger device increases risk, the observational evidence from the study by McGovern et al. represents the most salient quantitative estimate—an elevated odds ratio of 3.8. Calculating a commonly used epidemiological statistic, the attributable risk in the exposed (RR-1/RR), the estimate is 2.8/3.8 or 74%. With this magnitude of excess risk, the Bair Hugger device would constitute a substantial contributing cause.

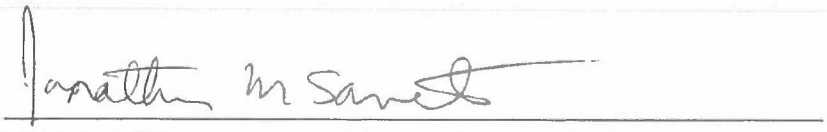


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Figure 1: Hypothetical Example of Three Sufficient Causes of Disease From: Rothman KJ, Greenland S. Causation and causal inference in epidemiology. Am J Public Health. 2005; 95 Suppl 1:S144-50.

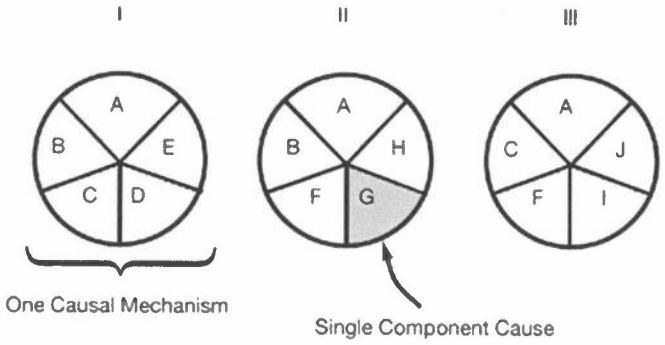
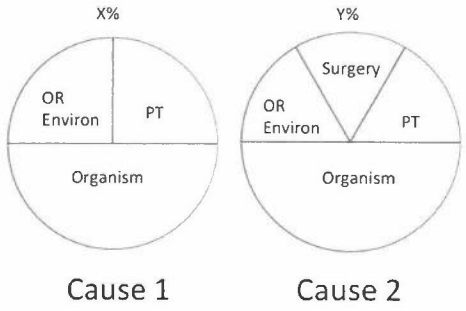


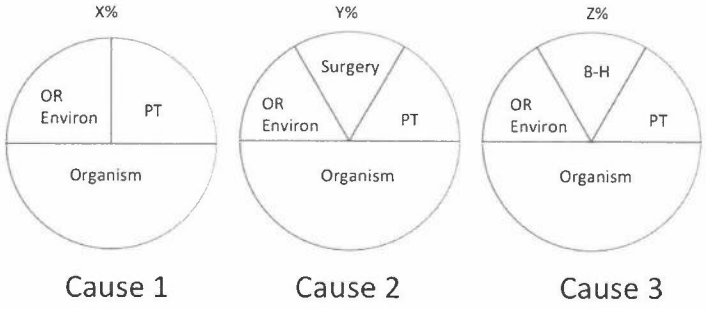
Figure 2: Adaptation of Sufficient Component Cause Model to Deep Joint Infection Risk

A: Causal Mechanisms for Deep Joint Infection without Bair-Hugger Devices



These causal pies are hypothetical and are not drawn to scale.
OR Environ = Operating Room Environment; PT = Patient;
Surgery = Surgical procedure factors

B: Causal Mechanisms for Deep Joint Infection with Bair-Hugger Devices



These causal pies are hypothetical and are not drawn to scale.
OR Environ = Operating Room Environment; PT = Patient; B-H = Bair Hugger Device
Surgery = Surgical procedure factors

Figure 3: Mechanisms by which the Bair Hugger Device Increases Risk for Deep Joint Infection

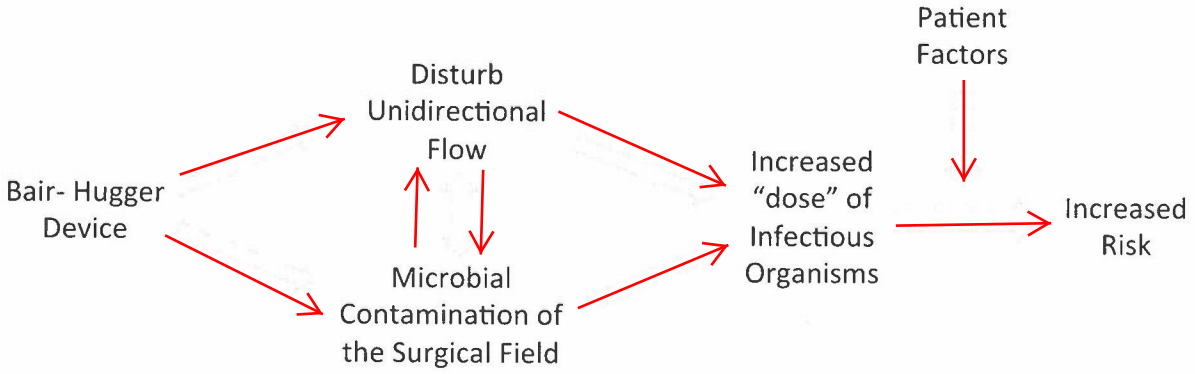


Table 1. Guidelines for causal inference. Data from the 1964 Smoking and Health: Report of the Advisory Committee to the Surgeon General and from Hill 1965

US Surgeon General Report's criteria	Hill's criteria
Consistency of association	Strength
Strength of association	Consistency
Specificity of association	Specificity
Temporal relationship of association	Temporality
Coherence of association	Biological gradient
	Coherence
	Experiment

Table 2. Studies comparing mean temperature differences of potential surgical site contamination with comparison of Bair Hugger device versus control

Reference	Indicator	Bair Hugger Device	Comparison	Ratio
Legg et al. 2012	Temperature difference (°C)	1.1°C	Radiant warming 0.4°C	$p < 0.001$
Desari et al. 2012	Temperature difference (°C)	Floor 0°C Table 0°C Head 0°C Shoulders 1.9°C Surgical site (abdomen) 3.8°C Knees 7.1°C	Hot Dog (an over-body conductive blanket) Floor 0°C Table 0°C Head 0°C Shoulders 1.8°C Surgical site (abdomen) 1.0°C Knees 3.9°C Inditherm (an under-body resistive mattress) Floor 0°C Table 0°C Head 0°C Shoulders 0.2°C Surgical site (abdomen) 0.1°C Knees 0.4°C	Hot Dog +2.73; $p < 0.001$ Inditherm +3.63; $p < 0.001$

Table 3. Studies comparing indicators of potential surgical site contamination with comparison of Bair Hugger device versus control

McGovern et al. 2011	Neutral-buoyancy detergent bubbles counted by photos	half drape 68 laid-down 3 full-drape 0	conductive warming half-drape 0 laid-down 0 full-drape 1	Infinite for half-drape and laid-down and 0 for full-drape
Legg et al. 2012	HandiLaz handheld particle counter over surgical site	0.3 microns mean=1038.2	0.3 microns 274.8 (no warming)	3.78 (p=0.0087)
Legg et al. 2013	0.3 micron glycerol particles measured over surgical site with HandiLaz particle counter	2.174x106/m3	2x103 /m3 (no warming used)	2,174
Belani et al. 2013	Neutrally buoyant detergent bubbles counted by a sequence of 10 photographs taken at 10-second intervals per experimental run	Modeled estimate of 132.5	modeled estimate of 0.48 for conductive warming	276